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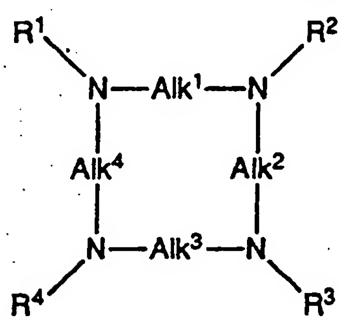
(54) Tetra-aza macrocycles; processes for their preparation, and their use in magnetic resonance imaging.

(57) Metal complex of tetra-aza macrocycles of formula (1)



(1)

wherein Alk^1, Alk^2, Alk^3 and Alk^4, which may be the same or different, is each a C_{1-4}alkylene chain optionally substituted by one or more optionally substituted C_{1-6} alkyl groups; and R^1, R^2, R^3 and R^4 which may be the same or different is each a hydrogen atom or a group AlkR^5 where Alk is an optionally substituted straight or branched C_{1-6} alkyl group and R^5 is a hydrogen atom or a $-CO_2H$, $-CONR^6R^7$ [where R^6 and R^7, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group] or $-P(X^1)(X^2R^8)R^9$ group where X^1 and X^2, which may be the same or different is each an oxygen or sulphur atom, R^8 is a hydrogen atom or an alkyl group and R^9 is an aliphatic, aromatic or heteroaromatic group, with the proviso that at least two of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ or one of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ and at least one of the remaining groups R^1, R^2, R^3 and R^4 is a group $-AlkCO_2H$ or $-AlkCONR^6R^7$, or a salt thereof, for use as contrast agents in nuclear magnetic resonance imaging are described.

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Field of the Invention

This invention relates to tetra-aza macrocycles, to metal complexes thereof to processes for their preparation and to their use in magnetic resonance imaging.

Background to the Invention

Proton nuclear magnetic resonance (NMR) is extensively used as a means of chemical analysis. In recent years it has also found increasing use as an imaging technique, in particular for use in examination of the human body, where it has many advantages over other imaging methods [see, for example, Andrew, E.R., Acc. Chem. Res. 16. 114-122 (1983)].

For effective NMR imaging it is usually desirable to employ a paramagnetic agent, more commonly known as a contrast agent, to enhance the sensitivity of the technique and to reduce imaging time. Numerous paramagnetic agents are available [see, for example Brasch R.C., Radiology 147. 781-788 (1983)].

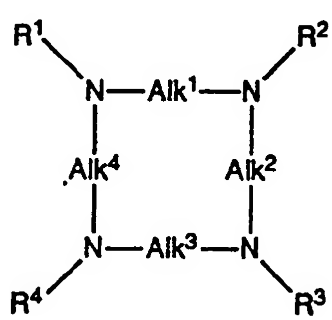
A contrast agent that has recently received much attention is gadolinium, which has an unusually large magnetic moment, which efficiently relaxes magnetic nuclei. A major problem with gadolinium, however, is its toxicity to animals, and to attempt to reduce this, gadolinium has been complexed with a number of organic molecules, including diethylenetriaminepentaacetic acid (DTPA) [see for example Weinmann, H.J., et al Am. J. Roentgenology 142, 619-624, (1984)], tetraazacyclododecanetetraacetic acid (DOTA) [Bousquet, J.C., et al Radiology 166., 693-698 (1988)] and other polyamines [see for example U.S. Patent Specification No. 4639365]. Of these, Gd-DTPA is probably the best known paramagnetic contrast agent currently in clinical use, while it has recently been suggested that Gd-DOTA, with an in vitro stability five orders of magnitude greater than that of Gd-DTPA, could also be a clinically useful contrast agent [Bousquet, J.C. et al (1988) ibid].

Despite the success of Gd-DTPA and Gd-DOTA, there are instances when they are of limited use [see for example Adzamli et al J. Med. Chem. 32, 139-144 (1989)] and there is still a general need for a contrast agent which has good enhancement of proton relaxation times, while remaining stable in vivo, and which has low toxicity at doses appropriate for contrast enhancement in a wide variety of applications. In particular, contrast agents are required which can also be used in the imaging of certain organs, such as the brain, and other tissues or lesions which are not particularly accessible to agents such as Gd-DTPA or Gd-DOTA. In such instances, large doses of Gd-DTPA or Gd-DOTA may be required to achieve satisfactory imaging, and toxicity can then begin to be a problem, with the result that the agent is no longer diagnostically useful.

There are a number of reported attempts to provide improved DOTA analogues for NMR imaging, in which a use of different ring structures and/or ring substituents has been employed [see for example European Patent Specifications Nos. 305320, 352218, 355097, 365412 and 391766, and International Patent Specifications Nos. WO89/00557 and WO89/05802].

We have now found a new class of tetra-aza macrocycles containing at least one phosphinic acid side-chain, which are capable of forming highly stable complexes with elements such as gadolinium. Compounds of the class, when complexed to gadolinium, also enhance proton relaxation times and are thus of use in NMR diagnostic techniques. The compounds have excellent metal binding properties, and advantageous solubility characteristics, and are of use in a wide variety of NMR imaging applications.

Thus according to one aspect of the invention we provide a metal complex of a compound of formula (1)



(1)

wherein Alk^1, Alk^2, Alk^3 and Alk^4, which may be the same or different, is each a C_{1-4}alkyl n chain optionally substituted by one or more optionally substituted C_{1-6} alkyl groups; and R^1, R^2, R^3 and R^4 which may be the same or different is each a hydrogen atom or a group $AlkR^5$ where Alk is an optionally substituted straight or

branched C_{1-6} alkyl group and R^5 is a hydrogen atom or a $-CO_2H$, $-CONR^6R^7$ [where R^6 and R^7, which may b the same or different, is each a hydrogen atom or a C_{1-6} alkyl group] or $-P(X^1)(X^2R^8)R^9$ group where X^1 and X^2, which may be th same or different is each an xyg n r sulphur atom, R^8 is a hydrog n atom or an alkyl group and R^9 is an aliphatic, aromatic or heteroaromatic group, with th provis that at least two of R^1, R^2, R^3 and R^4 is a group -Alk $P(X^1)(X^2R^8)R^9$ or one of R^1, R^2, R^3 and R^4 is a group -Alk $P(X^1)(X^2R^8)R^9$ and at least one of the remaining groups R^1, R^2, R^3 and R^4 is a group $-AlkCO_2H$ or $-AlkCONR^6R^7$, or a salt thereof, for use as a contrast agent for nuclear magnetic resonance imaging.

It will be appreciated that formula (1) [and, where appropriate, the following formulae herein], is intended to cover all stereoisomers of the compounds concerned, including mixtures thereof.

The term "nuclear magnetic resonance" is abbreviated hereinafter to NMR.

Alk^1, Alk^2, Alk^3 and Alk^4 in the compounds of formula (1) may each be a chain $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$ or $-(CH_2)_4-$, optionally substituted by one or more C_{1-6}alkyl, [e.g. methyl or ethyl] groups, optionally substituted by one or more groups, such as by one or more hydroxy groups. Examples of substituted Alk^1, Alk^2, Alk^3 and Alk^4 chains include $-CH_2-CH(CH_3)-$, $-CH_2-C(CH_3)_2-$ or $-CH_2-CH(CH_2OH)-$.

In the compounds for use according to the invention, alkyl groups represented by R^6, R^7 or R^8 may be straight or branched chain groups and may be for example C_{1-6} alkyl groups such methyl, ethyl, n-propyl or i-propyl groups.

The group $CONR^6R^7$ when present in compounds of formula (1) may be for example $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-CONHCH_2CH_3$ or $-CON(CH_2CH_3)_2$.

Alk in compounds of formula (1) may be for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group. Such groups may be substituted, for example, by one or more atoms or groups as described herein below. Particular substituents include for example one or more halogen atoms, e.g. fluorine or chlorine atoms, or hydroxy or phenyl groups.

Thus, particular examples of the group $AlkR^5$ include $-CH_2CO_2H$, $-CH_2CONH_2$, $-CH_2CONHCH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2$-phenyl and $-CH_2P(X^1)(X^2R^8)R^9$, especially $-CH_2P(O)(X^2H)R^9$.

When the group R^9 in compounds of formula (1) is an aliphatic group it may be for example an optionally substituted straight or branched chain alkyl, alkenyl, alkynyl, alkoxy or alkylthio group, optionally interrupted by one or more heteroatoms, or a cycloalkyl or cycloalkenyl group. When R^9 is an aromatic group it may be for example an aryl or aralkyl group. Heteroaromatic groups represented by R^9 include heteroaryl and heteroaralkyl groups.

Thus, for example, R^9 may be an optionally substituted C_{1-10} alkyl (e.g. C_{1-6} alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl) C_{2-10}alkenyl (e.g. C_{2-6} alkenyl such as ethene, propene, 1-butene, 2-butene, or 2-methylpropene), C_{2-10}alkynyl (e.g. C_{2-6} alkynyl such as ethyne, propyne, 1-butyne, or 2-butyne) C_{1-10} alkoxy (e.g. C_{1-6}alkoxy such as methoxy, ethoxy, n-propoxy, i-proproxy, n-butoxy, s-butoxy, or t-butoxy) or C_{1-10}alkylthio (e.g. C_{1-6}alkylthio such as methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, s-butylthio, or t-butylthio) group optionally interrupted by one or more heteroatoms selected from -O-, -S- or $-NR^{10}$ (where R^{10} is a hydrogen atom or a C_{1-6} alkyl group), for example an alkoxyalkyl (e.g. methoxymethyl), alkylthioalkyl (e.g. methylthiomethyl) or alkoxyalkoxy or alkylthioalkoxy (e.g. methoxymethoxy or methylthiomethoxy) group; or a C_{3-8} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or C_{4-8} cycloalkenyl (e.g. cyclobutene, cyclopentene, cyclohexene, cyclohexadiene) group.

When R^9 is an aryl group it may be for example an optionally substituted C_{6-12}aryl group such as an optionally substituted phenyl or naphyl group.

When R^9 is an aralkyl group it may be for example an optionally substituted $C_{6-12}arC_{1-6}$alkyl group for example a phenC_{1-6}alkyl group such as benzyl or phenethyl.

When R^9 is a heteroaryl group it may be for example an optionally substituted C_{4-10}heteroaryl group containing one or more heteroatoms selected from -O-, -NH- or -S- for example a pyridyl, furanyl or thienyl group.

When R^9 is a heteroaralkyl group it may be for example an optionally substituted $C_{4-10}heteroarC_{1-6}$alkyl group containing one or more heteroatoms selected from -O-, -NH-, or -S- for example a thienyl C_{1-6}alkyl (e.g. thienylmethyl) or pyridylC_{1-6}alkyl (e.g. pyridylmethyl) group.

Optional substituents which may be pres nt on alkyl, alkoxy, aryl, aralkyl, heteroaryl or heteroaralkyl groups in compounds of formula (1) [for example in Alk and R^9, where present] include halog n atoms .g. chlorine, bromine, fluorine or iodine atoms, or ne or m re groups selected from hydroxyl, C_{1-6} alkyl [e.g. methyl, ethyl] trihalomethyl [e.g. trifluoromethyl], C_{1-6} alkoxy [e.g. meth xy or ethoxy], C_{1-6}alkylthio, [.g. m thylthio], hydroxyC_{1-6}alkyl, [e.g. hydroxymethyl or hydroxypropyl] polyhydroxyC_{1-6}alkyl, amino [$-NH_2$], substituted amin , [e.g. $NR^{11}R^{12}$ where R^{11} is a hydrogen atom or a C_{1-6} alkyl group and R^{12} is a C_{1-6} alkyl group, such as

methylamino or dimethylamino], nitro, cyano, carboxyl, $-CONR^6R^7$ [e.g. $-CONH_2$], $-SO_2NR^6R^7$ [e.g. SO_2NH_2] aryl, [e.g. phenyl], or C_{3-8}cycloalkyl [e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl] groups.

Metal complexes of compounds of formula (1) include complexes wherein the metal is a transition metal with an atomic number 21 to 29, 42, 43, 44 or 75, or a lanthanide with an atomic number 57 to 70 or a Group III element with atomic number 5, 13, 31, 49 and 81 and is generally di- or tripositive and has a coordination number 6 or greater, especially 8. Examples of such metals include manganese, iron, terbium, europium, dysprosium, scandium, gadolinium, gallium and indium.

Salts of compounds of formula (1) or the metal complexes thereof include salts with inorganic or organic bases, for example alkali metal or alkaline earth metal salts such as lithium, sodium, potassium, magnesium or calcium salts; amine salts, such as those from primary, secondary or tertiary amines, for example ethanolamine, diethanolamine, morpholine, glucamine, N-methylglucamine or N,N-dimethylglucamine salts; and amino acid salts such as lysine, arginine and ornithine salts.

Particularly useful compounds of formula (1) are those wherein Alk^1, Alk^2, Alk^3 and Alk^4 is each a $-(CH_2)_2-$ chain.

Another useful group of compounds of formula (1) is that wherein R^1, R^2, R^3 and R^4 is each a group $-AlkP(X^1)(X^2R^8)R^9$, particularly a group $-AlkP(O)(X^2H)R^9$, especially $-AlkP(O)(OH)R^9$. Particularly useful compounds of this type are those wherein each of R^1, R^2, R^3 and R^4 is a $CH_2P(O)(OH)R^9$ group. Another important group of compounds of this type is that wherein R^9 is an alkyl group, particularly a methyl group, or an optionally substituted phenyl group.

In another preference, each of the groups R^1, R^2, and R^3 may be for example a group $-AlkP(X^1)(X^2R^8)R^9$ and R^4 may be a hydrogen atom or a group -Alk, $-AlkCO_2H$ or $-AlkCONR^6R^7$. Thus for example each of the groups R^1, R^2 and R^3 may be a group $-CH_2P(O)(OR^8)R^9$ especially $-CH_2P(O)(OH)R^9$, e.g. where R^9 is an alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group or an aralkyl group such as a benzyl group or an optionally substituted phenyl group and R^4 may be a hydrogen atom or a group $-CH_2CH(OH)CH_3$, $-CH_2CO_2H$ or $-CH_2CONR^6R^7$, especially $-CH_2CONH_2$, $-CH_2CONHCH_3$ or $-CH_2CON(CH_3)_2$.

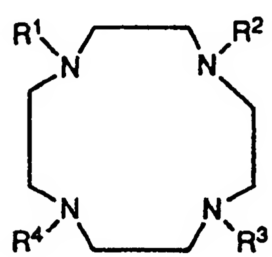
In still another preference, each of the groups R^1, R^2 and R^3 may be a group $-AlkP(S)(OR^8)R^9$, e.g. $-AlkP(S)(OH)R^9$ such as $-CH_2P(S)(OH)R^9$ where R^9 is an alkyl group such as a methyl group, or an optionally substituted phenyl group and R^4 may be a hydrogen atom or a group Alk, e.g. $-CH_2CH(OH)CH_3$, $AlkCO_2H$, e.g. $-CH_2CO_2H$ or $AlkCONR^6R^7$, e.g. $-CH_2CONR^6R^7$ such as $-CH_2CONH_2$, $-CH_2CONHCH_3$ or $-CH_2CON(CH_3)_2$.

One group of compounds for use according to the invention are the metal complexes of compounds of formula (1) wherein Alk^1, Alk^2, Alk^3, Alk^4, R^1,R^2, R^3 and R^4 are as defined for formula (1) with the further proviso that the group R^9 in at least one of the groups $-AlkP(X^1)(X^2R^8)R^9$ is as defined for formula (1) but is other than an unsubstituted alkyl or alkoxy group.

A further useful group of compounds for use according to the invention are the gadolinium complexes of the compounds of formula (1) and the salts thereof.

The following formulae (1a)-(1c) define various preferred groups of compounds for use according to the invention. It will be appreciated that the detailed definitions given above for each of the groups R^1-R^5 and Alk in respect of formula (1) also apply to these formulae.

A particularly useful group of compounds for use according to the invention are the metal complexes of the compounds of formula (1a):

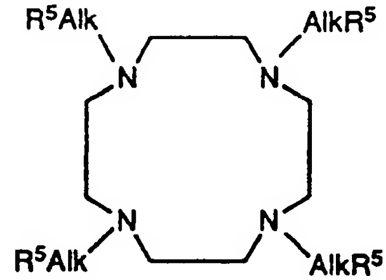


(1a)

wherein R^1, R^2, and R^3 which may be the sam or different is each a group $-AlkP(X^1)(X^2R^8)R^9$ and R^4 is a hydrogen atom or a group -Alk, $-AlkCO_2H$, $-AlkCONR^6R^7$ or $-AlkP(X^1)(X^2R^8)R^9$, wh r Alk, X^1, X^2, R^6, R^7, R^8 and R^9 are as previously defin d; and th salts thereof.

In the compounds of formula (1a), the group $-AlkP(X^1)(X^2R^8)R^9$ when present is preferably a group $-AlkP(O)(OH)R^9$, especially $-CH_2P(O)(OH)R^9$, particularly where R^9 is an aliphatic or aryl group, such as an optionally substituted alkyl or phenyl group.

A useful group of compounds of formula (1a) has th formula (1b):



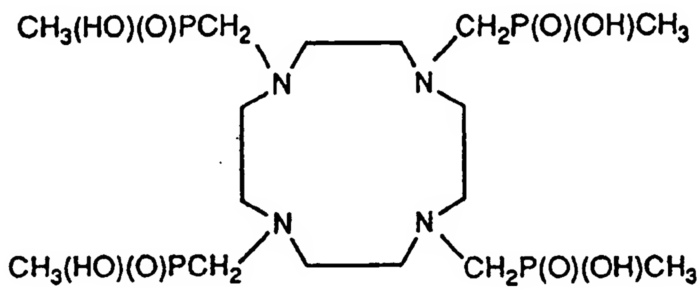
(1b)

wherein Alk is as defined for formula (1) and each R^5 group is a -P(O)(X^2R^8)R^9 group, where X^2, R^8 and R^9 are as previously defined; and the metal complexes and/or salts thereof.

Particularly useful compounds of formula (1b) are those wherein Alk is $-CH_2-$. Compounds of formula (1b) wherein R^5 is a group -P(O)(X^2H)R^9, especially a group -P(O)(OH)R^9 where R^9 is an aliphatic or aryl group, particularly an optionally substituted alkyl or phenyl group, such as a group $-P(O)(OH)CH_3$, or -P(O)(OH)Ph [where Ph is phenyl or substituted phenyl] and the metal complexes and/or salts thereof are particularly useful. Compounds of this type where Alk is $-CH_2-$ are also important.

Gadolinium complexes of the compounds of formula (1b) are especially useful.

Particularly useful compounds for use according to the invention are the metal complexes of the compound of formula (1c):



(1c)

and the salts thereof.

The gadolinium complex of the compounds of formula (1c) and the salts thereof is a particularly useful compound.

The metal complexes of the compounds of formula (1) may be used employing conventional NMR procedures and apparatus [see for example H.J. Weinmann et al Am. J. Roentgenology ibid and U.S. Patent Specifications Nos. 4374360, 4398148, 4409550, 4425547, 4442404 and 4450408].

Compounds of formula (1) may be employed for the preparation of contrast agents for use in NMR imaging, for example by complexation with an appropriate metal, as described herein. Thus according to another aspect of the invention we provide a compound of formula (1) or a salt thereof for use in the preparation of a contrast agent for NMR imaging.

The metal complexes of the compounds of formula (1) and the salts thereof may generally initially be formulated for use for administration to an animal, e.g. human subject using standard procedures. Thus according to a further aspect of the invention we provide a pharmaceutical composition comprising a metal complex of a compound of formula (1) or a salt together with one or more pharmaceutically acceptable carriers for use as a contrast agent for NMR imaging.

Suitable formulations include those adapted for oral or parenteral administration, e.g. by injection or infusion and may take the form of liquid preparations of metal complexes of the compounds of formula (1) and the salts thereof, such as soluti ns, suspensions, emulsions or syrups in oily or aqueous vehicles which may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the m tal complex may be in powder form for reconstitution with a suitable v hicle, e.g. sterile pyrogen-free water, or isotonic saline befor use.

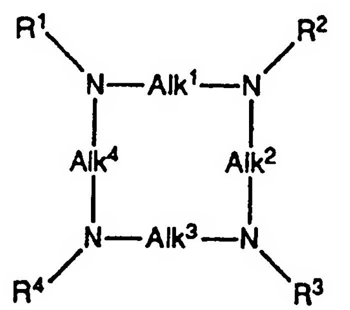
In yet another aspect of the invention, we provid th use of a metal complex f a compound of formula (1) or a salt thereof for the pr paration f a pharmaceutical composition for use in NMR imaging.

Standard procedures may be used for the preparation of compositions according to the invention, depending on the formulation chosen.

The metal complexes of the compounds of formula (1) and the salts thereof may be administered at any suitable dosage, depending on the nature of the target to be imaged. Thus according to a further aspect of the invention we provide a method of enhancing NMR contrast in an animal subject which includes administering to said subject an effective amount of a metal complex of a compound of formula (1) or a salt thereof.

In general, the complexes according to the invention may be administered in amounts of 0.001 to 5mMol/Kg.

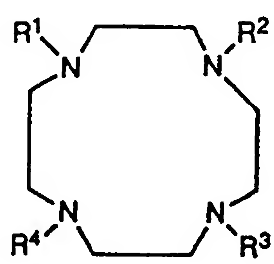
Certain compounds of formula (1) are new and form a further aspect of the invention. Thus, according to another aspect of the invention we provide a compound of formula (2)



(2)

wherein Alk^1, Alk^2, Alk^3 and Alk^4, which may be the same or different, is each a C_{1-4}alkylene chain optionally substituted by one or more optionally substituted C_{1-6} alkyl groups; and R^1, R^2, R^3 and R^4 which may be the same or different is each a hydrogen atom or a group $AlkR^5$ where Alk is an optionally substituted straight or branched C_{1-6} alkyl group and R^5 is a hydrogen atom or a $-CO_2H$, $-CONR^6R^7$ [where R^6 and R^7, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group] or $-P(X^1)(X^2R^8)R^9$ group where X^1 and X^2, which may be the same or different is each an oxygen or sulphur atom, R^8 is a hydrogen atom or an alkyl group and R^9 is an aliphatic, aromatic or heteroaromatic group, with the proviso that at least two of R^1, R^2, R^3 and R^4 is a group $-Alk\,P(X^1)(X^2R^8)R^9$ or one of R^1, R^2, R^3 and R^4 is a group $-Alk\,P(X^1)(X^2R^8)R^9$ and at least one of the remaining groups R^1, R^2, R^3 and R^4 is a group $-AlkCO_2H$ or $-AlkCONR^6R^7$, and R^9 in at least one of the groups $-AlkP(X^1)(X^2R^8)R^9$ is an aliphatic, aromatic or heteroaromatic group but is not an unsubstituted alkyl or alkoxy group when R^1, R^2, R^3 and R^4 are the same and the metal complexes and/or salts thereof.

A particular useful group of compounds of formula (2) has the formula (2a)



(2a)

wherein R^1, R^2, and R^3 which may be the same or different is each a group $AlkP(X^1)(X^2R^8)R^9$ and R^4 is a hydrogen atom or a group -Alk, $-AlkCO_2H$, $-AlkCONR^6R^7$ [where Alk, X^1, X^2, R^6, R^7, R^8 and R^9 are as defined previously] or R^4 is a group $-AlkP(X^1)(X^2R^8)R^9$ [where Alk, X^1, X^2, R^8, and R^9 are as previously defined with the proviso that R^9 is not an unsubstituted alkyl group] and the salts thereof.

A useful group of compounds of formula (2a) is that wherein R^1, R^2, R^3 and R^4 is each a group $-AlkP(X^1)(X^2R^8)R^9$ wherein R^9 is an aryl group. Particular compounds of this type includ $-CH_2P(O)(OH)R^9$, where R^9 is an aryl group. Aryl groups represented by R^9 include C_{6-12} aryl groups such as optionally substituted phenyl or napthyl groups. Optional substituents may b those described previously and may in particular be on or more halogen atoms, e.g. chlorine, bromin fluorine or iodine atoms, C_{1-6} alkyl groups such as methyl groups, trihalomethyl groups, such as trifluoromethyl groups or carboxyl groups.

A further useful group of compounds of formula (2a) is that wherein R^1, R^2 and R^3 is ach a group -

$AlkP(X^1)(X^2R^8)R^9$ [where Alk; X^1, X^2,R^8 and R^9 ar as defined in the pr c ding paragraph] and R^4 is a hydrogen atom or a group -Alk, $-AlkCO_2H$, or $-AlkCONR^6R^7$. In particular, R^4 may be a group $-CH_2CH(OH)CH_3$, $-CH_2CO_2H$, $-CH_2CONH_2$ $-CH_2CONHCH_3$, or $-CH_2CON(CH_3)_2$.

The compounds of formula (2) hav xcellent metal binding properties and in particular form stable complexes with metals such as gadolinium. The compounds also have good solubility characteristics and when complexed with a metal such as gadolinium are of particular use as contrast agents in NMR imaging. The suitability of such complexes for use as contrast agents may initially determined in test animals, using standard procedures, for example as described hereinafter in relation to Figure 1.

It will be appreciated that the various preferences expressed above in relation to the compounds of formula (1) for use as contrast agents also apply to the compounds of formula (2) as just defined.

Compounds of formula (1) may be prepared by the following processes. Unless otherwise defined, the various groups Alk and Alk^1-Alk^4, X^1, X^2, and R^1-R^9 as they appear in the description below are to be understood to have the meanings described above. The following processes clearly also apply to the preparation of compounds of formula (2).

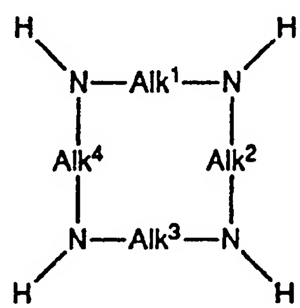
Metal complexes for use according to the invention may be prepared by reacting a compound of formula (1) or a salt thereof with a metal salt (e.g. a nitrate, halide, such as a chloride, acetate, carbonate or sulphate) or a metal oxide.

The reaction may be performed in an appropriate solvent, for example an aqueous or non-aqueous solvent (e.g. acetonitrile, acetone, propylene carbonate, dimethylformamide or dimethylsulphoxide) at any suitable temperature from 0°C to 100°C such as 10°C to 85°C.

Salts of compounds of formula (1) may be prepared by reacting a compound of formula (1) with a base in an appropriate solvent, for example an aqueous or non-aqueous solvent as described above, at any suitable temperature from O°C to 100°C.

Compounds of formula (1) in which one or more R^1, R^2, R^3 and R^4 is each a group $AlkP(X^1)(X^2H)R^9$ may be prepared by interconversion of a corresponding compound of formula (1) in which one or more of R^1, R^2, R^3 and R^4 is each a group $AlkP(X^1)(X^2R^8)R^9$ [where R^8 is an alkyl group] by treatment with an acid, for example an inorganic acid such as hydrochloric acid at an elevated temperature, for example the reflux temperature, or by treatment with a base, for example an inorganic base such as potassium hydroxide.

Compounds of formula (1) in which R^1, R^2, R^3 and R^4 is each a group $-AlkP(X^1)(X^2R^8)R^9$ [where R^8 is an alkyl group] may be prepared by reaction of a compound of formula (2).



(3)

with a phosphine $R^9P(X^1Alk^5)(X^2R^8)$ where R^8 is as just defined and Alk^5 is an alkyl group, for example a methyl or ethyl group] in the presence of formaldehyde, paraformaldehyde or an aldehyde RCHO (where R is a C_{1-5}-alkyl group).

The reaction may be performed in a solvent, for example an organic solvent such as an ether, e.g. a cyclic ether such as tetrahydrofuran at an elevated temperature e.g. the reflux temperature.

Where it is desired to prepare a compound of formula (1) where at least one of R^1, R^2, R^3 and R^4 is not a group $AlkP(X^1)(X^2R^8)R^7$, this may be achieved by initially selectively N-protecting a compound of formula (3) or a precursor thereof using an appropriate amine protecting group(s) for example a p-toluenesulphonyl group in accordance with conventional practice [see for example International Patent Specification No. WO89/01476]. Th resulting N-protected compound of formula (3) may then b reacted with a reagent R^5AlkD (where R^5 is other than a $-P(X^1)(X^2R^8)R^9$ group and D is a displaceable group such as a halogen, e.g. chlorine, atom or a sulphonyloxy group, e.g. a m thanesulphonyloxy group) in a solvent such as water or an organic solvent such as an amide e.g. dimethylformamide in the presence of a base, e.g. an inorganic base such as an alkali metal carbonate, e.g. potassium or caesium carbonate, at an elevated temperature [in this reaction, any $-CO_2H$ group

present in R^5AlkD may need to be protected, for example as an ester, .g. a methyl ester, th acid may be regenerated after the desired reaction is complete, for example by hydrolysis using an acid such as sulphuric acid]. After reaction with R^5AlkD, the resulting derivatised compound of formula (3) may be deprot cted using conventional procedures, and then further reacted with a phosphine $R^9P(X^1Alk^5)(X^2R^8)$ as described above to yield the desired compound of formula (1).

In a further variation, a compound of formula (3) may be reacted with a phosphine $R^9P(X^1\ Alk^5)(X^2R^8)$ as previously described, and the desired di- or tri-substituted product isolated, e.g. by chromatography [using e.g. alumina in a solvent such as dichloromethane]. The di- or tri-substituted product may then be reacted with a reagent R^5AlkD as desrcibed above to yield the desired product of formula (1).

When a compound of formula (1) is desired where one or two of R^1, R^2, R^3 and R^4 is a hydrogen atom, this may be obtained using a N-protected intermediate of formula (3) as described above, and reacting this with a phosphine $R^9P(X^1\ Alk^5)(X^2R^8)$, followed by deprotection to yield the appropriate -N-H compound.

Intermediates of formula (3) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Description of the Drawing

Figure 1 illustrates the results of an imaging study performed with the complex of Example 2 in rats inoculated in the thigh region with sarcoma cells.

In the figure, A is an image of the sarcoma (arrowed) before the aministration of the complex; B is an image after administration and C is a subtraction image obtained from A and B clearly showing the sarcoma.

The images were obtained at 65MHz (1.5 Tesla) using a dose of complex of 0.1 mM/Kg.

Acute Toxicity

The complexes for use in the invention are substantially non-toxic at imaging doses. Thus for example the complex of Example 2 caused no deaths when intravenously administered to mice at single doses up to 12mM/Kg body weight.

The following Examples illustrate the preparation of compounds for use according to the invention.

Example 1

Preparation of the compound of formula 1(c) and the corresponding tetra ethyl ester.

(a) To a solution of 1, 4, 7, 10- tetrazacyclododecane (0.5g) in dry tetrahydrofuran (30ml) was added diethoxymethylphosphine (2.37g) and paraformaldehyde (1.13g) and the mixture was heated to reflux with azeotropic removal of water (Soxhlet, 3A sieves). After 18h solvent was removed under reduced pressure and the residue was purified by chromatography on alumina (0 2% CH_3OH in CH_2Cl_2) to yield a pale yellow oil (948mg) Rf 0.5 (5% $MeOH/CH_2Cl:Al_2O_3$). δp ($CDCl_3$) 51.6, 51.8, 51.9, (diastereoisomers) δc ($CDCl_3$) 13.44 (d, J_{CP}91 Hz, PCH_3), 16.42 (CH_3), 54.18 (CH_2N ring), 54.30 (d, J_{CP} 110Hz, CH_2P), 59.82 (CH_2O). δ_H($CDCl_3$), 1.31 (12H, t, CH_3CH_2),1.57 (12H, d, J=13.7Hz, CH_3P), 2.64-3.07 (24H, mult., CH_2N), 4.07 (8H, dq, CH_2O). m/e (d.c.i.) 652(M^+), 533 ($M^+PC_3H_8O_2$).

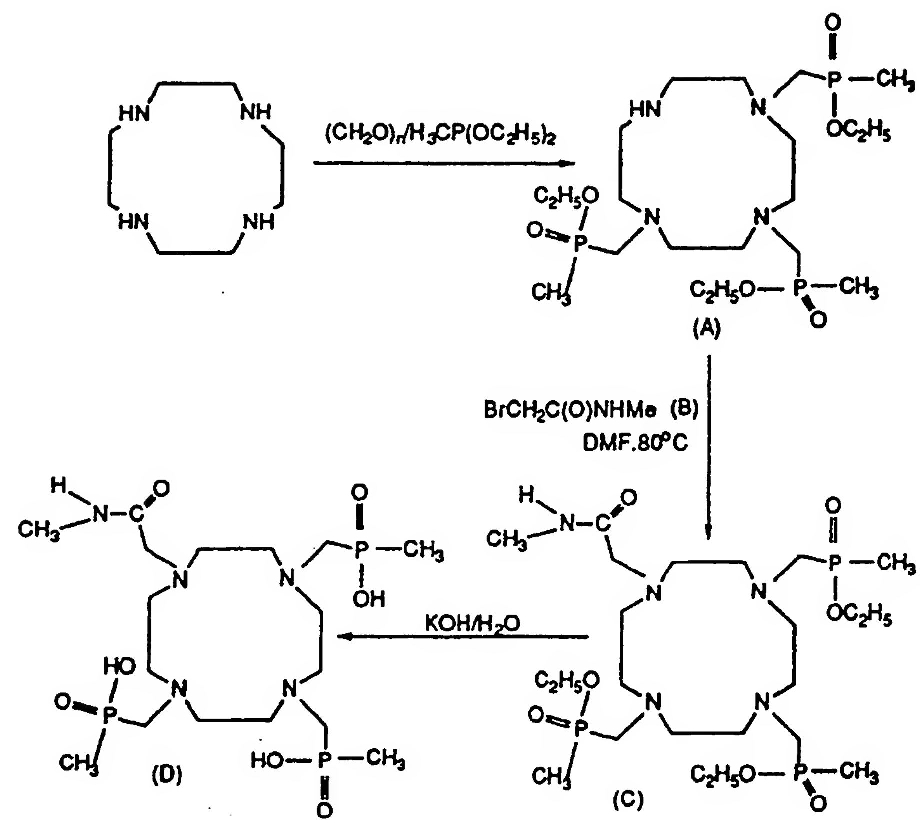
(b) The tetraester prepared in Part (a) (115mg) in hydrochloric acid (6M, 20ml) was heated to reflux (100°C) for 36h. After removal of solvent and drying under vacuum (40°C, 0.01 mmHg) the compound of formula 1(b) was obtained as a glassy foam. δ(D_2O) 41.03. δc(D_2O) 14.86 (d, J_{CP} 94Hz, CH_3P), 50.70 (CH_2N), 51.64 (d, J_{CP}, 118.3Hz, CH_2) δH(D_2O) 1.41 (12H, d, J=14.1 Hz, CH_3P), 3.37 (24H, Br, CH_2N) m/e (negative FAB, glycerol) 540^+ (M^+), 539 (M^+-1), 538 (M^+-2).

Example 2

Preparation of the Gadolinium Complex of the Compound of Formula (1c)

T a solution of the tetraphosphinic acid prepared in Example 1(b) (400mg) in MilliQ water (10ml) was added gadolinium oxide (133mg) and the suspension was heated at 70°C for 2h. After removal f solvent the gadolinium complex of the compound of f rmula 1(b) was btained as a colourless glass m/e (negative FAB, glycerol) 696, 694, 693, 692, 691.

Example 3



Reaction scheme for the synthesis of Compound (D)

Synthesis of (A)

1,4,7,10-Tetra-azacyclododecane (1 g, 5.8mmol) was stirred in dry tetrahydrofuran (50cm³) under an argon atmosphere. To this was added paraformaldehyde (0.6g) and methyldiethoxyphosphine (2.6g). The mixture was heated under reflux over molecular sieves for about 18 hrs to give a cloudy solution. The solution was filtered and the solvent was evaporated under vacuum. The product was purified by column chromatography using alumina with a gradient from dichloromethane to 4% methanol-dichloromethane as eluent (Rf product = 0.28 5% methanoldichloromethane), ^{1}HNMR ($\delta CDCl_3$); 9H (t, O-CH_2-$\underline{CH_3}$) 1.4ppm, 9H (d, P-$\underline{CH_3}$) 1.53ppm, 22H (broad, m, $\underline{CH_2}$-$\underline{CH_2}$ and N-$\underline{CH_2}$) centred at 2.8 ppm, 6H (m, O-$\underline{CH_2}$) centred at 4.1 ppm, m/z 533 (100, M^++1), 425 (89, M^+-P(O)(OC_2H_5)(CH_3)).

Synthesis of (B)

Methyl amine hydrochloride (13.5g) was added to a stirring solution of 1,2-dichloroethane (150 cm³) and sodium hydroxide (16g in 25 cm³ of water). The mixture was cooled to -10°C using an ice/salt/ethanol bath. Bromoacetyl bromide (31.5g) in 1,2-dichloromethane (25cm³) was added to the solution with a rate to keep the temperature of the solution below -10°C. After the addition, the mixture was warmed to room temperature, the organic layer was separated, dried with magnesium sulphate and the solvent was evaporated under vacuum to give a pale brown solid. The product was isolated as white crystals by sublimation (25°C, 0.05mmHg). ^{1}HNMR (δ, $CDCl_3$); 3H (d, H-N-$\underline{CH_3}$) 2.87 ppm, 2H (s, Br-$\underline{CH_2}$) 3.9 ppm, 1H (broad, s, $\underline{H}$-N)6.6ppm.

Synthesis of (C)

The compound (A) (0.1g) and potassium carbonate (0.03g, 1.8 x 10^{-4}mol) were stirred in anhydrous dimethyl formamide (5cm³) under an argon atmosphere. To this was added compound B (0.03g, 1.8 x 10^{-4}mol)

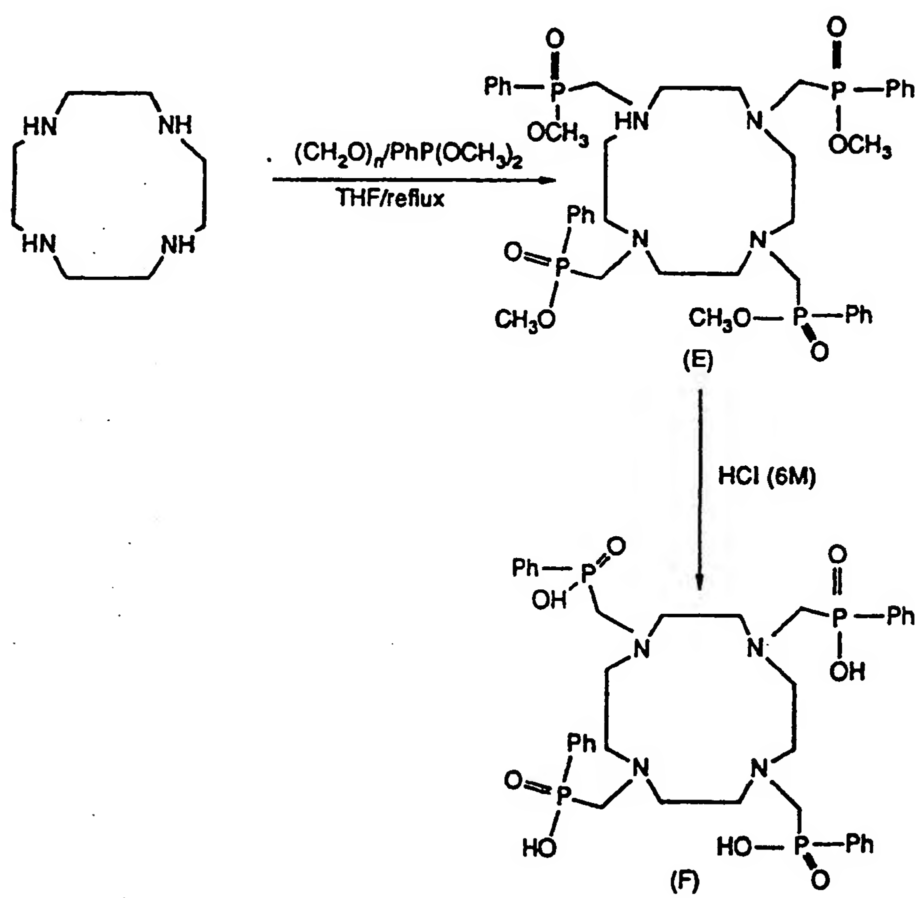
and the mixture was heated at 80°C for about 16 hrs to give a cloudy solution. Th solv nt was evaporated and the residual mass was redissolved in dicvhloromethane wan filtered to give a clear solution. The solvent was evaporated and the crude product was purified by column chromatography using alumina with a gradient from dichloromethane to 2% methanol-dichloromethane as eluent (R_f product = 0.6, 10% methanol - dichloromethane). ^{1}HMNR (δ, $CDCl_3$); 9H (t, CH_2-$C\underline{H}_3$) 1.31 ppm, 9H (d, P-$C\underline{H}_3$) 1.5 ppm, 27H (broad, m,$C\underline{H}_2$-$C\underline{H}_2$ and N-$C\underline{H}_2$ and N-$C\underline{H}_3$) centred at 2.85 ppm, 6H (q, P-O-$C\underline{H}_2$) 4.06 ppm, 1H (broad, s, N-$\underline{H}$) 8.2 ppm, m/z 604 (100, M^++1), 12.5, M^+-$CH_2C(O)NHMe$).

Synthesis of (D)

The compound C (0.05g, 5.9 x 10^{-4}mol) was treated with KOH/H_2O and the ^{1}HNMR spectrum of the reaction mixture comprised resonances corresponds to ethanol and the hydrolysed product D, ^{1}HNMR (δD_2O); 9H (d, P-$C\underline{H}_3$) 1.2 ppm, 27H (broad, m, $C\underline{H}_2$-$C\underline{H}_2$, N-$C\underline{H}_2$ and N-$C\underline{H}_3$) centred at 2.66 ppm.

Compounds of formula (1) in which R^1, R^2 and R^3 is each - $CH_2P(O)((OH)CH_3$ and R^4 is -$CH_2CH(OH)CH_3$ or -$CH_2CH_2CH_2OH$ were prepared in similar fashion to compound (D) from compound (A) except that propylene oxide or ethylene oxide was used in place of compound (B).

Example 4



Reaction Scheme for the Synthesis of Compound(F).

Synthesis of (E)

1,4,7,10-Tetra-azacyclododecane (0.5g) was stirred in dry Tetrahydrofuran (30cm^3) under an argon atmosphere. To this was added paraformaldehyd (0.5g) and phenyldimethoxyphosphine (2.5g) and the mixtur was

heated und r reflux over molecular sieves for about 16 hrs to give a yellow cloudy soluti n. The solution was filtered and the solvent was evaporated und r vacuum. The crude product was purified by column chromatography using alumina with a gradient from dichloromethane to 2% methanol-dichloromethane (R_f product = 0.63 10% methanol-dichloromethane). ^{1}HNMR (δ $CDCl_3$); 16H (broad, m, $C\underline{H_2}$-$C\underline{H_2}$) centred at 2.42 ppm, 8H (broad, d, N-$C\underline{H_2}$-P) centred at 2,9 ppm, 12H (d, P-O-$C\underline{H_3}$) 3.55 ppm, 12H (m, Ph) 7.4ppm, 8H (m, Ph) 7.75 ppm, M/z 845 (100, M^++1).

Synthesis of (F)

The compound (E) (0.05g) was heated at 110°C with hydrochloric acid (6M) for 16 hrs and the solvent was evaporated to dryness in vacuo. ^{1}HNMR (δ, D_2O); 24H (broad, m) centred at 3.5 ppm, 20H (broad, m) centred at 24ppm, ^{31}P-(^{1}H)NMR; (broad) 21.5 ppm, pD=0.45

Example 4

Intermediate 1

Preparation of $HOCH_2P(O)(OH)(CH_2)_3NHCOPh$

To a solution of N-benzamido allylamine (7.47g) and hypophosphorus acid (8.66g, 50% solution) in dioxane (100ml) was added t-butlperoxide (0.4g) and the mixture was heated to reflux for 18h. Solvents were removed under reduced pressure and ^{1}HNMR analysis of the residuerevealed that the olefinic resonances had disappeared. The residue was redissolved in dioxane (50ml) and paraformaldehyde (25g) was added and the mixture heated to reflux for 72h. After removal of solvent the residue was chromatographed on silica (eluant 70% CH_2Cl_2, 25% methanol, 5% NH_4OH) to yield the ammonium salt of the title acid as pale yellow glass: δp (D_2O)+41.1 ppm; δc (D_2O) 170.04 (CONH), 134.0 ($C_5H_6\underline{C}CO$); 132.28, 128.98, 127.22 (CH), 59.73 (PCH_2OH, d, J_{CP} 99Hz); 41.01 ($CONHCH_2$); 25.12 ($P\underline{C}H_2CH_2$, d, J_{CP}=81 Hz); 22.03 ($PCH_2\underline{C}H_2CH_2NHCO$) δ_H (D_2O) 7.79 (2H, dd, ortho ArH), 7.57 (4H mult, NHCO +AZrH); 3.81 (2H, d, J=6 Hz, $P\underline{CH_2}OH$); 3.71 (2H, t, J=6.9Hz, CH_2NCO), 1.8 (4H, mult, PCH_2CH_2).

Intermediate 2

Preparation of $HOCH_2P(O)(OEt)(CH_2)_3NHCOPh$

To Intermediate 1 (5g) in distilled water (50ml) was added Dowex strong acid ion exchange resin (30g, H^+ form) and after filtration the filtrate was evaporated under reduced pressure and the residue treated with triethylorthoformate (25ml) and the mixture heated under argon at 90°C for 96h. After removal of $HC(OEt)_3$ under reduced pressure the residue was chromatographed on silica (CH_2Cl_2=5 to 10% methanol gradient) to yield a mixture of the desired alcohol ester and the mixed orthoformate ester. Treatment of this mixture with ethanol (50ml, 1 ml, concentrated HCl) followed heating to reflux (36H), evaporation and subsequent chromatographic purification as before yielded the title alcohol ester as a pale yellow oil, (4g). m/e (d.c.i.) 286 (M^++1). δp ($CDCl_3$) 53.7ppm δ_H ($CDCl_3$) 7.71 (2H, dd, ortho, CH), 7.25 (3H, mult, arom CH), 6.85 (1H, brt, NHCO), 4.05 (1H, brs OH), 3.81 (2H, dq, CH_2O), 3.70 (1H, br, d, CH_2OH); 3.31 (2H, t, $HN\underline{C}H_2$), 1.75 (4H, mult., PCH_2CH_2); 1.05 (3H, t, CH_3). δ_c ($CDCl_3/CD_3CO_2D$) 168.56 (CONH) 132.98 ($C_5H_6\underline{C}O$); 131.11, 127.82, 126.58 (CH); 56.16 (PCH_2OH, d, J_{CP}=90Hz); 20.33 (CH_2); 15.37 (CH_3).

Intermediate 3

Preparation of $MsOCH_2P(O)(OEt)(CH_2)_3NHCOPh$

To a suspension of Intermediate 2 (0.57g) in dry tetrahydrofuran (50ml) at 0°C was added triethylamine (1g) and methanesulphonyl chloride (1.14g) under argon). After 2h stirring, ethanol (5ml) was added and the mixture stirred for 20min at 0°C, s lvent removed under reduced pr ssure, and th residue tak n up in ethyl acetate (30ml), filtered and evaporated to giv a residue which was chromat graph d on silica gel (eluant 2 to 5% methanol in CH_2Cl_2) to yield the title mesylate as a colourless oil (390mg) m/e (δ.c.i, CH_2Cl_2) 364 (M^++1). δp ($CDCl_3$) 45.96 ppm. δ_c ($CDCl_3$) 168.6 (NHCO); 134.0 ($CH_5H_5\underline{C}CO$); 131.4, 128.4, 129.3 (CH); 62.2 ($PO\underline{C}H_2$), 61.2 ($P\underline{C}H_2OMs$, d, J_{CP}=70Hz); 39.62 ($CONH\underline{C}H_2$), 37.6 (OSO_2CH_3); 24.0 ($P\underline{C}H_2CH_2$, d, J_{PC}=100Hz); 21.2 (CH_2), 15.4 (CH_3)

(a) Preparation of a Compound of Formula (1) where R^1) is $-CH_2P(O)(OEt)(CH_2)_3NHCOPh$ and R^2, R^3 and R^4 is each -H

To a solution of 1, 4, 7, 10-t trazacyclododecane (0.16g) in dry dimethylformamide (25ml) was added potassium carbonate (0.13g) at 60°C and a solution of Intermediate 3 (0.167g) in dimethylformamide (15ml) over a period of 2h under N_2. After 64h, hplc analysis (CM300) revealed that reaction was not progressing and solvent was removed under reduced pressure. The crude residue was redissolved in dichloromethane (30ml), filtered and evaporated before purification on a CM-300 column to yield the title monoalkylated amine (0.05g) as a pale yellow oil. R_t = 8.2min (CM300 hplc). δ_H ($CDCl_3$) 1.30 (3H, t, J=76Hz, OCH_2CH_3), 1.97 (5H, mult, CH_2CH_2N+NH), 2.64-2.94 (20H, mult, CH_2P), 3.55 (2H, dt, $CONHCH_2$) 4.06 (2H, dq, OCH_2), 7.38-7.47 (3H, mult, aryl CH), 7.93 (2H, dd, orthoCH), 8.55 (1H, t, CONH). m/e (c.i.) 440 (M^++1) 394 (M^+-OC_2H_5)

(b) Preparation of a Compound of Formula (1) where R^1 is $-CH_2P(O)(OEt)(CH_2)_3NHCOPh$ and R^2, R^3, and R^4 is each $-CH_2P(O)(OEt)CH_3$

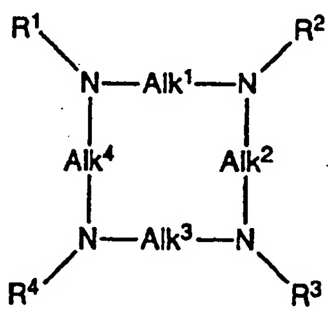
To a solution of the Compound of Example 1 (0.015g) in dry dimethylformamide (1 ml) was added potassium carbonate (16mg) and $MsOCH_2P(OEt)_2CH_3$ (25mg) under N_2. After heating to 80°C for 16h, t.l.c. (Al_2O_3) and hplc analysis (CM300) indicated no further reaction had occurred. After removal of solvent under reduced pressure, the residue was treated with dichloromethane (10ml) filtered and evaporated to yield a residue which was purified by chromatography on alumina (eluant 0 to 2% methanol in CH_2Cl_2) to give the title tetraester as a colourless oil (11 mg). R_t (CM300, hplc) 4.6min. δ_H ($CDCl_3$) 1.30 (12H, t, J=7.2, CH_3CH_2), 1.49 (9H, d+d+d, PCH_3), 1.80-3.70 (30H, mult., br., CH_2N+CH_2P+CH_2C) 4.05 (8H, dq, OCH_2), 7.39 (3H, mult, arylCH), 7.92 (2H, dd, ortho CH), 8.35 (1H, br, NHCO). m/e (c.i.) 800 (M^++1).

(c) Preparation of a Compound of Formula (1) where R^1 is $-CH_2P(O)(OH)(CH_2)_3\ NH_2$ and R^2, R^3, and R^4 is each $-CH_2P(O)(OH)CH_3$

Hydrolysis of the tetraester of Part (b) (6M hydrochloric acid, 110°C, 48h) afforded after removal of solvent the title amino-tetraacid δ_H ($CDCl_3$) 1.35 (9H, d), 1.55-1.85 (4H, m), 2.6-3.7 (30H, m), 7.35 (2H, d), 8.35 (2H, d).

Claims

1. A metal complex of a compound of formula (1)



(1)

wherein Alk^1, Alk^2, Alk^3 and Alk^4, which may be the same or different, is each a C_{1-4}alkylene chain optionally substituted by one or more optionally substituted C_{1-6} alkyl groups; and R^1, R^2, R^3 and R^4 which may be the same or different is each a hydrogen atom or a group $AlkR^5$ where Alk is an optionally substituted straight r branched C_{1-6} alkyl group and R^5 is a hydrogen atom or a $-CO_2H$, $-CONR^6R^7$ [where R^6 and R^7, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group] or $-P(X^1)(X^2R^8)R^9$ group where X^1 and X^2, which may be the same or different is each an oxygen or sulphur atom, R^8 is a hydrogen atom or an alkyl group and R^9 is an aliphatic, aromatic or heteroaromatic group, with th proviso that at least tw of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ or on of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ and at least one of the remaining groups R^1, R^2, R^3 and R^4 is a group $-AlkCO_2H$ or -Alk-

$CONR^6R^7$, or a salt thereof, for use as a contrast agent for nuclear magnetic resonance imaging.

2. A metal complex of a compound of formula (1) or a salt th reof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 1 wherein the metal is gadolinium.

3. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claims 1 or 2 wherein Alk^1, Alk^2, Alk^3 and Alk^4 is each a $-(CH_2)_2-$ chain.

4. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in any of the preceding claims wherein R^1, R^2, R^3 and R^4 is each a group $-AlkP(X^1)(X^2R^8)R^9$.

5. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claims 1-3 wherein the groups R^1, R^2 and R^3 is each a group $-AlkP(X^1)(X^2R^8)R^9$ and R^4 is a hydrogen atom or a group -Alk, $-AlkCO_2H$ or $-AlkCONR^6R^7$.

6. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 4 or Claim 5 wherein the group $-AlkP(X^1)(X^2R^8)R^9$ is $AlkP(O)(OH)R^9$.

7. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 6 wherein the group $-AlkP(O)(OH)R^9$ is $-CH_2P(O)(OH)R^9$.

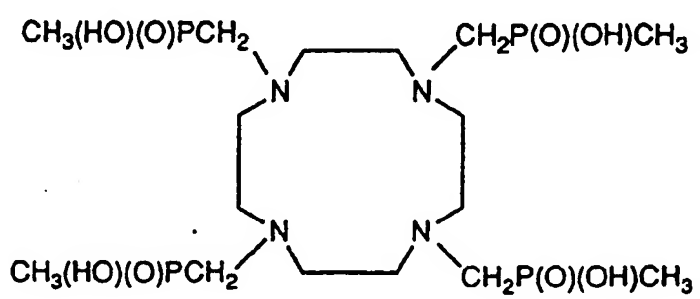
8. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 6 where R^9 is an optionally substituted alkyl group.

9. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 6 wherein R^9 is an aryl group.

10. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 9 wherein R^9 is an optionally substituted phenyl or naphthyl group.

11. A metal complex of a compound of formula (1) or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging as claimed in Claim 10 wherein R^9 is a phenyl group optionally substituted by one or more halogen atoms or groups selected from hydroxyl, C_{1-6} alkyl, trihalomethyl, C_{1-6} alkoxy, C_{1-6}alkylthio, hydroxyC_{1-6}alkyl, polyhydroxyC_{1-6}alkyl, amino [$-NH_2$], substituted amino, nitro, cyano, carboxyl, $-CONR^6R^7$, $-SO_2NR^6R^7$, aryl, or C_{3-8}cycloalkyl groups.

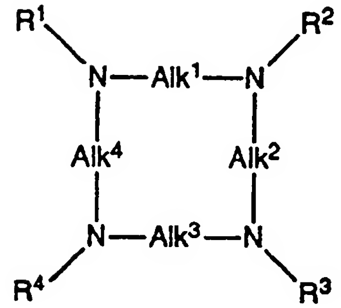
12. A metal complex of a compound of formula (1c)



(1c)

or a salt thereof for use as a contrast agent for nuclear magnetic resonance imaging.

13. A compound of formula (2)



(2)

wherein Alk^1, Alk^2, Alk^3 and Alk^4, which may be the same or different, is each a C_{1-4}alkylene chain optionally substituted by one or more optionally substituted C_{1-6} alkyl groups; and R^1, R^2, R^3 and R^4 which may be the same or different is each a hydrogen atom or a group $AlkR^5$ where Alk is an optionally substituted straight or branched C_{1-6} alkyl group and R^5 is a hydrogen atom or a $-CO_2H$, $-CONR^6R^7$ [where R^6 and R^7, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group] or $-P(X^1)(X^2R^8)R^9$ group where X^1 and X^2, which may be the same or different is each an oxygen or sulphur atom, R^8 is a hydrogen atom or an alkyl group and R^9 is an aliphatic, aromatic or heteroaromatic group, with the proviso that at least two of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ or one of R^1, R^2, R^3 and R^4 is a group $-Alk\ P(X^1)(X^2R^8)R^9$ and at least one of the remaining groups R^1, R^2, R^3 and R^4 is a group $-AlkCO_2H$ or $-Alk-CONR^6R^7$, and R^9 in at least one of the groups $-AlkP(X^1)(X^2R^8)R^9$ is an aliphatic, aromatic or heteroaromatic group but is not an unsubstituted alkyl or alkoxy group when R^1, R^2, R^3 and R^4 are the same and the metal complexes and/or salts thereof.

14. A compound according to Claim 13 wherein Alk^1, Alk^2, Alk^3 and Alk^4 is each a $-(CH_2)_2-$ chain.

15. A compound according to Claims 13 or 14 wherein R^1, R^2, R^3 and R^4 is each a group $-AlkP(X^1)(X^2R^8)R^9$.

16. A compound according to Claims 13 or 14 wherein R^1, R^2 and R^3 is each a group $-AlkP(X^1)(X^2R^8)R^9$ and R^4 is a hydrogen atom or a group Alk, $-AlkCO_2H$ or $-AlkCONR^6R^7$.

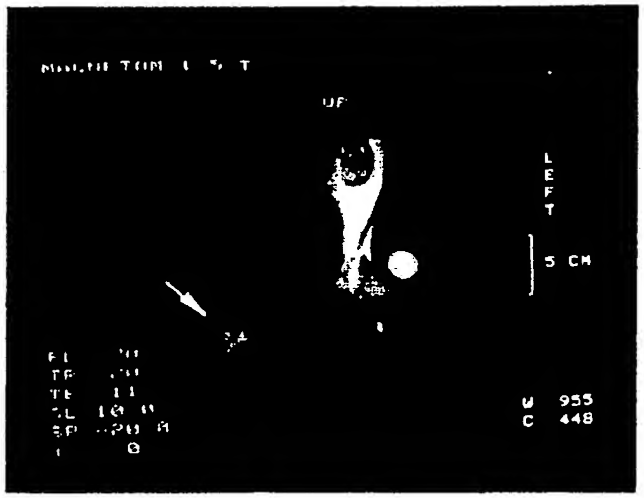
17. A compound according to Claim 15 or Claim 16 wherein $-AlkP(X^1)(X^2R^8)R^9$ is $-AlkP(O)(OH)R^9$.

18. A compound according to Claim 17 wherein $-AlkP(O)(OH)R^9$ is $-CH_2P(O)(OH)R^9$

19. A compound according to any of Claims 13-18 wherein R^9 is an aryl group.

20. A compound according to Claim 19 wherein R^9 is an optionally substituted phenyl or napthyl group.

21. A compound according to Claim 20 wherein R^9 is a phenyl group optionally substituted by by one or morehalogen atoms or groups selected from hydroxyl, C_{1-6} alkyl, trihalomethyl, C_{1-6} alkoxy, C_{1-6}alkylthio, hydroxyC_{1-6}alkyl, polyhydroxyC_{1-6}alkyl, amino [$-NH_2$], substituted amino, nitro, cyano, carboxyl, $-CONR^6R^7$, $-SO_2NR^6R^7$, aryl, or C_{3-8}cycloalkyl groups.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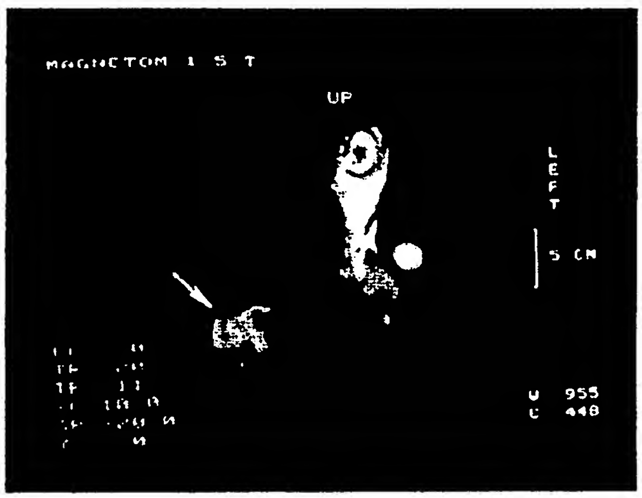
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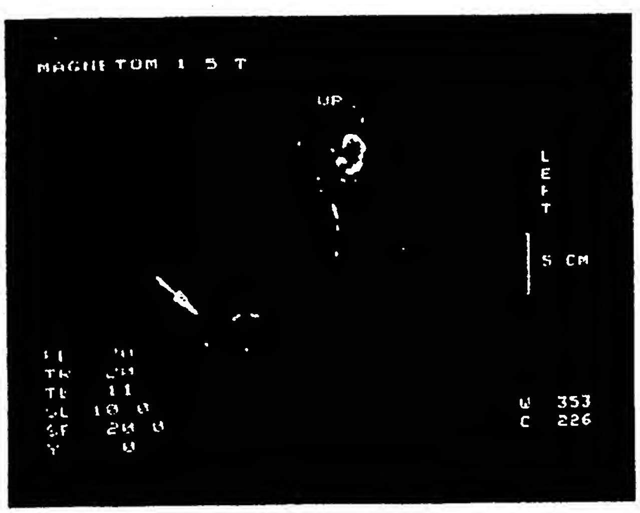
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FIG. 1